UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,049	11/01/2005	Eva Kontsekova	SONN:066US	5434

32425 7590 07/10/2006

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/521,049	KONTSEKOVA ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03-16-2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/01/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAIL ACTION

Applicant's amendment to claims 17-33, and cancellation of claims 1-16, in response to the Requirements for Restrictions is acknowledged. Applicant's election with traverse of Group I (i.e., claims 17-24) in the response filed on 05-03-2006 is acknowledged.

Response to arguments

Applicant's arguments in view of the official restriction/election requirements of 04/05/06 have been respectfully reconsidered. In response to applicant's assertion that inventions of Groups I-III relate to a single inventive concept under PCT Rule 13.3 because they posses the same special technical feature of a non-human transgenic animal of claim, Examiner has considered the argument persuasive. As such, restriction to inventions of Groups I-III is withdrawn.

Therefore, Claims 17-33 are pending in the instant application to which the following grounds of rejection are applicable.

Claim objections

Claim 17 objected to because of the following informalities. Claim 17 recites that a transgenic non-human animal comprises a DNA construct comprising a cDNA molecule coding for N- and C-terminally truncated tau molecules. It is clear that said tau molecules are peptides or proteins. However, the claim as written, discloses that said tau molecules have truncated at least 30 nucleotides downstream of the star codon. It is unclear how a truncated tau molecule comprising amino acids can have at least 30 truncated nucleotides.

Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite in its recitation of " the minimally truncated tau core" since it is unclear how this term is defined, what its metes and bounds are, or to what the term is directed towards. It is not clear what the minimally truncated tau core comprises in addition to a protein fragment encoded by SEQ ID No. 9.

Claim 25 and dependent claims 26 and 27 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: the administration and evaluation of a candidate to a transgenic non-human animal of claim 17 for the detection and measurement of changes in said animal.

**It is noted that dependent claims 18-33 rely upon claim 17, and are potentially rejectable since these claims recite all the limitations of claim 17. However, amending claim 17 can obviate the potential rejection of these claims.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-33 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The present invention provides a transgenic rat all of whose germ and/or somatic cells comprise a group of specifically truncated isoforms of tau protein engineered genetically that corresponds to those present exclusively in Alzheimer's disease (AD) brain, capable of inducing AD pathology in transgenic animals (p. 13, paragraphs 1 and 2 and Fig. 1).

Specifically, the as-filed specification teaches by exemplification a transgenic rat expressing double truncated tau molecules. Moreover, analysis of genomic DNA obtained from F1 generation reveals that transgenes were heritable since they were also identified in the offspring of the parental generation (p. 22, paragraph 4). Though it is clear that a transgenic rat was created, the as-filed specification does not provide a reasonable disclosure of a transgenic rat whose cloned genes comprise a construct coding for truncated Alzheimer's tau molecules. Thus it is unclear if the transgenic rat disclosed comprises a construct as recited in claim 17, or a construct other than the one recited in claim 17, or a construct from the group disclosed in Fig. 1.

Moreover, even if a transgenic rat was created comprising one sequence as recited in claim 1, the as-filed specification fails to describe sufficient relevant identifying characteristics for any other transgenic rats comprising any construct coding for truncated Alzheimer's tau molecules (e.g., how to select or use other gene constructs expressing Alzheimer's tau proteins or properties of constructs containing genes coding for Alzheimer's tau proteins desirable to make and use in a transgenic rat).

Further, the specification fails to describe sufficient identifying characteristics to extrapolate results from a transgenic rat to any other transgenic non-human animal as broadly claimed, containing a DNA construct which has neurofibrilary pathology producing activity when expressed in brain cells of said a transgenic animals.

The specification discloses in Fig. 3 the genotyping of transgenic founder animals and F1 generation of transgenic animals by genomic DNA amplification of truncated tau forms from a transgenic animal (p. 22, last paragraph). Moreover, the specification teaches expression of Alzheimer's tau proteins in the brain of transgenic rats by quantifying specific expression of said proteins by Western analysis and localizing by immunohistochemistry said proteins in rat brain tissue sections (pp. 24 and 25).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

The breadth of the claims

Claims 17 its dependent claims 18-33 are directed to a transgenic non-human animal comprising a DNA construct comprising a cDNA molecule coding for N- and C-terminally truncated tau molecules, which have neurofibrillary (NF) pathology producing activity when expressed in brain cells of said transgenic animals Moreover, claims 17 its dependent claims 18-33, are further drawn to a screening assay system and validation system using said transgenic non-human animal and a method for assaying the efficacy of substances or therapies using said transgenic non-human animal.

When read in light of the instant specification, the claimed recombinant DNA expression construct used for the generation of a transgenic rat (page 6, paragraph 3 and the entire

specification) is not described sufficiently in the as-filed specification. It should be noted that enablement requires the specification to teach how to make and use the claimed invention. With respect to claims drawn to a transgenic non-human animal as encompassed in claim 17 and methods of using said animal as screening and validation assay systems (claim 25) and a method for assaying the efficacy of substances or therapies (claim 28), the instant specification fails to provide sufficient guidance for a skilled artisan on how to use a transgenic non-human animal as claimed broadly for the reasons set forth below.

The state of the prior art and the unpredictable of the prior art

At about the effective filing date of the present application (07/09/2003), the transgenic art was and continues to be unpredictable with respect to transgene behavior *in vivo*. Transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) (Sanders Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2). This is supported by the teachings of Hammer et al. (J. Anim. Sci. 63:269-278, 1986). They reported the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pp. 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Hammer at al. (Cell, 1990, 63: 1099-112) provides similar insight into unexpected phenotypes in transgenic models when he teaches that the art of transgenics is unpredictable even when using the same construct to make

transgenic rats and mice (p. 1099, column 2, lines 20-28). These results can be explained by a plethora of intrinsic differences across the species, such as promoter/enhancer elements, co-regulatory factors that may be present in one species and not another, or the existence of redundant pathways in one species versus another that can lead to differences in phenotype. Sigmund (Arterioscler Thromb Vasc Biol, 2000, pp. 1425- 1429) corroborates the lack of predictability of phenotypes in transgenic models when he discloses that the phenotype caused by a specific genetic modification is strongly influenced by genes unlinked to the targeted locus. Sigmund discloses that even strain differences between mice carrying the same construct can profoundly influence the phenotype (Arterioscler Thromb Vasc Biol, 2000, p. 1425, col. 1, paragraph 2):

> "For example, whereas deletion of p53 tumor suppressor gene causes a dramatic increase in the frequency of tumor formation in those mice compared to the wild type, the type of tumors formed, their number per animal, and age of tumor onset vary in different genetic backgrounds."

Logan et al., (1999, Clinical and Experimental Pharmacology and Physiology, p. 1021, col. 2, paragraph 2) further support the unpredictability of the transgenic phenotype when he anticipates that the challenge in the development of transgenic animals in not in the process, but the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level. Additionally, Sanders Williams et al., (J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph) teach that adaptive modifications may also confound the interpretation of phenotypes.

With regard to the ability to transfer genes into the germ line of any-non-human animal as broadly claimed, prior art teaches the challenging issues faced in accessing and manipulating the germ lines of non-human animal. For example, Shuman (Experientia 47, pp. 897-905, 1991)

teaches that the avian technology for gene transfer for production of transgenic birds has not progressed as much as mammalian gene transfer, in part, by the avian reproductive and embryonic developmental system (p. 897, col. 1, paragraph 1). Further, Shuman states that avian gene transfer technology, as any new technology, research, development and application will require a stepwise approach that includes considerable testing and evaluation (p. 904, col. 1, paragraph 1).

Guidance in the Specification and working examples

The specification discloses in Fig. 3 the genotyping of transgenic founders animal and F1 generation of transgenic animals by genomic DNA amplification of truncated tau forms from a transgenic animal (p. 22, last paragraph). Moreover, the specification teaches expression of Alzheimer's tau proteins in the brain of transgenic rats by Western analysis and localizes by immunohistochemistry said proteins brain tissue sections (pp. 24 and 25). Further, the specification contemplates the use of the transgenic animals for *in vitro* and *in vivo* systems for the study of drug candidates on cell architecture, cell division and apoptosis as well as morphology of primary cultured neurons, and of organelle movement (p. 25, paragraph 1, and FIG. 9).

The instant specification is not found to be enabling, because there is not sufficient relevant disclosure of a transgenic rat comprising the tau cDNA molecule as encompassed in claim 17, since the DNA construct use to produce a transgenic rat is not sufficiently disclosed in the as-filed specification. Additionally, the instant specification fails to teach how to make and use any other transgenic non-human animals comprising constructs containing genes coding for Alzheimer's tau proteins as encompassed by claim 17. Moreover, there is not correlation among

the phenotypes associated with Alzheimer's disease (e.g., hypertension, diabetes, hypercholesterolemia) such that one of skilled in the art could make and use a transgenic non-human animals in any of the contemplated uses. As enablement requires the specification to teach how to make and use the claimed invention, based on the instant disclosure a skilled artisan would not know how to make and use the claimed transgenic mice since the DNA construct embraced by claim 1 is not described with sufficient relevant identifying characteristic to use and make any other transgenic rats, let alone any other transgenic non-human animals as broadly claimed. Particularly in light of the state of the transgenic art which was and continues to be highly unpredictable with respect to the incorporation and expression of a transgene and the result of such incorporation to cause a desired phenotype in any species of animal, as discussed above.

Also, as discussed above, the level and specificity of a specific transgene as well as the resulting phenotype of a transgenic animal are directly dependent on a specific transgene construct. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in a transgene construct as well as the specificity of transgene integration into a genome are all important factors in controlling the expression of a transgene in the production of a transgenic animal which exhibits a resulting phenotype.

While the instant specification teaches that transgene expression was detected for expression Alzheimer's tau proteins in the brain of transgenic rats by Western analysis and corresponding proteins were localized by immunohistochemistry tissue sections, the specification fails to provide any correlation between expression of any Alzheimer's tau proteins in rat with any useful phenotype (e.g., hypertension, diabetes, hypercholesterolemia) or

characteristics because the instant specification is completely silent in this regard. Similarly, there is no correlation for association between expression of any derivative of the Alzheimer's tau proteins in rat with any relevant characteristics or useful phenotype. At the effective filing date of the present application, the prior art did not provide such guidance, thus it is incumbent upon the instant specification to do so. In the absence of such guidance provided by the instant specification and given the state and unpredictability of the relevant art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

With regard to the breadth of a transgenic rat, a recombinant DNA construct and methods of using these materials as claimed, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

With regard to claimed embodiments directed to a transgenic non-human animal the comprising any cDNA construct coding for any N- and C-terminally truncated tau protein

molecules comprising a minimally truncated tau core, there is a high degree of unpredictability associated with the making and using of such embodiments. The instant specification fails to teach which specific encoded amino acids to be substituted, deleted or inserted within the minimally truncated tau core, at which positions and in which combinations such that the encoded polypeptide derivative for N- and C-terminally truncated tau gene is still functional to yield results contemplated by Applicant. The relationship between the sequence of a peptide or polypeptide and its tertiary structure associated for its activity is not well understood and is not predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994). Moreover, in discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study (Page 6, Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Therefore, in the absence of sufficient guidance provided by the instant specification, it would therefore have required undue for one skilled in the art to make and use the instant broadly claimed invention.

Conclusion

In conclusion, the disclosed information from the as-filed application plus the state of the prior art is not deemed sufficient to reasonably convey to one of ordinary skill in the art that the Specification is reasonably enabling for the full breadth of the claim at the time the invention was made. Such is because the instant specification fails to sufficiently disclose how to make and use a transgenic non-human animal comprising the tau cDNA molecule as embraced in claim 17. It is unclear if the transgenic rat disclosed comprises a construct as recited in claim 17, or a

construct other than the one recited in claim 17, or a construct from the group disclosed in Fig. 1. Moreover, the instant specification fails to teach of any other transgenic variant rats, let alone any non-human transgenic animals, with any useful phenotype or characteristics and any methods of using said transgenic non-human animal. Because of lack of working examples, insufficient guidance and direction in the specification, the inherent unpredictability in the art, the state of the art and the nature of the invention, one of ordinary skill in the Art to would be required to perform a large amount of experimentation to make an/or use the invention claimed by the Applicant.

Conclusion

Claims 17-33 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776 or the examiner's supervisor, Nguyen Dave, can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PATENT EXAMINER

Maria Leavitt, PhD
Patent Examiner P/1633
Remsen 2B55
Phone: 571-272-1085
Email: maria.leavitt@uspto.gov